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L10 L11 L12 L4 L5 L6 L7 L7 61 BIOTECHNO, 66589 13789 28 S (THREE (W) S L1 AND L2 I CANCERLIT, ESBIOBASE' ENTERED AT 13:33:43 ON 16 OCT 2000 S IMPDH OR (INOSINE (W) MONOPHOSPHATE (W) DEHYDROGENASE?) S PYOGENES AND L1 DUP REM L8 DUP REM L3 L1 AND (STREPTOCOC? OR PYOGENES) L4 AND L7 REM L11 (0 DUPLICATES REMOVED) AND L2 AND L5

AND ((CRYSTAL OR X-RAY OR (X(W)RAY)) (5m, CAND (CRYSTAL OR X-RAY OR (X(W)RAY)) AND ((CRYSTAL OR X-RAY OR (X(W)RAY)) (3W) STRUCTUR?) (24 DUPLICATES REMOVED) DIMENSIONAL (W) STRUCTUR?) OR (3D STRUCTUR?) Ξ (3W) STRUCTUR?) STRUCTU CABA, OR,(I

ΑB PRAI TI DN Ä Method to identify specific
monophosphate * of exogenous WO 1998-IB2109 WO-9933996 the pJF118EH expression vector. illustrate the utility of the invention, can be expressed in a functional form in identification of specific purine nucleotide synthesis enzyme, This invention relates to methods to identify specific inhibitors of PATENT NO English Patent CODEN: The University of Chicago, 131:83979 1999:464100 essential 1997-997758 9915022 **Streptococcus*** Int identification GH, X X Ä, enzyme CAPLUS R.; Huberman CAPLUS NO, KIND 19971224 19981223 important œχ, found in all free-living organisms as a control component COPYRIGHT 2000 ACS 1999071 DATE 19990708 GB, USA for the expression inhibitors ***pyogenes*** inhibitors of gp, therapeutic RO, A variety of eukaryotic or prokaryotic RU, wz, ð δ APPLICATION NO. GM, ¥ SD, BR, the coding sequence of human and 1998-IB2109 a recombinant host cell. any 1999target AZ, 33 -15022 'n, SG 'n the methods allows * IMPDH * $\mathbf{I}\mathbf{S}$ invention allows the from DATE 19981223 19981223 K2 SK Ħ *** IMPDH *** humans to CF, SL, were cloned into ď. Ņ, enzyme which Utilization X Ϋ́

> AU eukaryotic
> properties
> ***IMPDH*** a target fo monovalent Journal code: CO2. ISSN: U.L. ______
> Journal code: CO2. ISSN: U.L. ______ ANSWER 3 OF hydrolysis o been identified. guanine nucleotide biosynthesis. Journal code: CO2. ISSN: 0929-8673. Hedstrom ***IMPDH*** is a tetramer with its four subunits related by a crystallographic 4-fold axis. The protein is composed of two domains:.
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> . flap as an essential catalytic element and indicate there are significant differences in the catalytic environment of bacterial and mammalian ****TMDRU**** reminiscent reduction of Biology Center at Argonne's Advanced Photon between the bacteria mammalian these differences, synchrotron radiat: pathogenic agents, we basis for the enzyme that BIOCHEMISTRY release immunosuppressive, attractive target for acid and the Journal code Zhang R; * * * HMPDH * * * * * IMPDH * * ***pyogenes*** iscent of glyceraldehyde-3-phosphate dehydrogenase. Substrates bind ***IMPDH*** in a random order, hydride transfer is fast and NADH se precedes hydrolysis of E-XMP*. The hydrolysis of E-XMP* is. ۲ OF. for Evans ressive, anticancer and antiviral chemotherapy, and may also be or antimicrobial agents. ***IMPDH*** is activated by cations, and one monovalent cation binding site appears to have lified. The mechanism of ***IMPDH*** involves formation and bacterium have expressed and characterized rganisms will * * * IMPDH * * * radiation from the undulator beamline (19ID) catalyzes the ics and crystal structure of bacterial inosine-5'-e dehydrogenase.
> ns G; Rotella F J; Westbrook E M; Beno D; Huberman bacterial and mammalian f a covalent enzyme intermediate (E-XMP *) in a reaction enzymes. However, the lack of the differences Km for NAD (1180 microM) exemplify some of the differences making it and mammalian ***IMPDH*** enzymes, making it and mammalian ***IMPDH*** NAD to NADH. This reaction is the rate-limiting that the biochemical and kinetic characteristics of S.
> *** ***IMPDH*** are similar to other bacterial * * IMPDH * * * evaluation of Collart F R. inhibitors MEDLINE * * * deh (1999 contribute.to MEDLINE catalyzes **dehydrogenase*** £ Ø dehydrogenase*** Apr 13) 38 (15) 4691-700. antimicrobial agents. determined the crystal. monophosphate*** ***Streptococcus** first step unique to GTP synthesis. To provide of ***IMPDH*** inhibitors as antimination of the synthesis and the synthesis and the synthesis. with the known partial structures from provide an explanation of their distinct the catalytic environment of bacterial and enzymes. Comparison of the structure of the design of specific bacterial (1999 Jul) 6 (7) 545-60. * * * HUGWI * * * lack of sensitivity to mycophenolic mechanism of action and inhibition. inhibitors as antimicrobial ****IMPDH*** from the To evaluate the basis for Source. S. Beno D; Huberman E; ***pyogenes*** is a proven DUPLICATE obtained with Ref: of the Structural ***pyogenes** 89 step target for the concomitant our n an

CURRENT Journal code: Collart Zhang R; Differential ANSWER 4 OF ***dehydrogenase*** MEDICINAL CHEMISTRY, code: C02. ISSN: 092 Evans G; signatures of bacterial and mammalian genase*** enzymes. signatures of bacterial and mammalian MEDLINE Rotella F; Westbrook E; Huberman E; ISSN: 0929-8673. enzymes. (1999 Jul) 6 3 537-43. DUPLICATE * * * IMP * * * Joachimiak A;

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signatures associated with bacterial or eukaryotic development process include mutagenesis. have a enzymes. used enzymes, suggesting characteristics that are different than the mammal identification kinetic applications may be extended to the development of antimicrobial agents me of de novo guanine nucleotid clinical utility as antiviral, sequence alignments role differences between. The essential nature of this enzyme suggests its therapeutic These of antimicrobial agents. 'n * * * HUGWI * * * Candidate bacterial sequence signatures identified by this catalysis using information derived from the bacterial of agents that specifically target the bacterial enzyme.
alignments of ***IMPDH*** proteins to identify sequence selections were regions ***dehydrogenase*** amino acid conservation associated with the ***IMPDH*** crystal structures and site-specific nucleotide further refined to discern those may e synthesis. ***IMPDH*** inh.
anticancer or immunosuppressive is a prerequisite for the rational ₩e suggest that the biochemical and be an attractive proteins to identify sequence mammalian **) is an essential ***IMPDH*** inhibit and kinetic * * * IMPDH * * * target for likely inhibitors and

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phylogenetic groups. Elucidation of the

enzyme and the foundation

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catalytic mechanism highly specific

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agents. Recently, a number of crystal structures obecome available. These include structures of the has led use or Borrelia burgdorferi enzymes. susceptibility to metabolic adenine dinucleotide). substrate site (e.g. ribavirin. Tritrichomonas foetus, monophosphate. * * * IMPDH * * * NAD-dependent oxidation of inosine ! **Inosine*** as two under to the search for potentially development. These isoforms, Several classes ၉. () the ***monophosphate*** active 1.1.1.205) is All suffer olic inactivation. To one of which (type ***Streptococcus*** site Each structure crystallizes as a include agents that bind at either 0f located partly from some degree of recognized as an important target structures of * * * IMPDH * * * 5 monophosphate acid and thiazole-4-carboxamide therapy. The finding that II) is induced in tumor effective isoform-specia *dehydrogenase*** at. human type II, * * * IMPDH * * *pyogenes** inhibitors are isoform-specific toxicity and/or ***HMPMI*** (IMP) to xanthosine * * * IMPDH * * * tetramer of hamster, catalyzes Mott cells, for

AU SO IT TI Cloning, sequence analysis and expression of ***streptococcal*** qual garage GENE, Cloning, sequence analysis and ***streptococcal*** guaB g Ashbaugh ANSWER 6 OF 7 ***monophosphate*** (1995 Ď Nov 7) Wessels MEDLINE 165 **3** 1 aB gene encoding
dehydrogenase 57 - 60. expression of the ***inosine*** group A DUPLICATE

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active protein of coli guaB open reading cloned a group function of * HDGWI * * * * * IMPDH * ***Inosine * * monopho in E C ø heterologous bacterial. tant restored ***IMPDH*** activity, confirming the the gene product and demonstrating that the GAS enzyme is 93 amino acids. Expression of the GAS guaB in an Escherichia tant restored ***IMPDH*** activity, confirming the sphate** frame similar The GAS guaB consists of 1479 ***streptococcal*** (GAS) DNA fragment containing an similar to other bacterial guab genes encoding ***monophosphate** ***dehydrogenase*** ***dehydrogenase*** nucleotides encoding a Σe

here A simple method for the rapid determination of the stereospecificity of NAD-dependent dehydrogenases applied to mammalian ***IMP***

dehydrogenase and bacterial NADH peroxidase with a microdistn. enzyme from The stereospecificity of 1.1.1.205) from 2 different Biochim. Marquez, Cooney, any NAD-dependent dehydrogenase. obtained NAD-dependent dehydrogenases applied to mammalian A simple met CODEN: ANSWER ***dehydrogenase** **Streptococcus*** demonstrated BBACA Davi 5) from 2 different sources was detd. from murine lymphoblasts and from Escom 2 very different species. In add og F Biophys. Victor hod for the rapid determination of the stereospecificity dehydrogenases applied to mammalian ***IMP*** d; Hamel, Ernest; Cohen, Marvin; ISSN: CAPLUS that alc. dehydrogenase and NADH peroxidase Acta (1987), SN: 0006-3002 *** faecalis), used as auxiliary enzymes, in combin procedure, may rapidly det. the stereospecificity of COPYRIGHT 2000 ACS and bacterial NADH peroxidase.

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***dehydrogenase* 916(1), 89-93 In addn. Escherichia coli Kang, The enzyme the studies described Gil J.; .Dalal, prepns. were in combination

DN AN S AU Fcollart@anl.gov BIOCHEMISTRY, (1 Center for Mechanistic Biology and Biotechnology, Joachimiak Zhang Characteristics and 99218077 Laboratory, inosine-5'-monophosphate dehydrogenase. 1999218077 **R**, 1 of Evans 9700 South Cass Avenue, Collart F (1999 Apr 13) MEDLINE MEDLINE G; Rotella F J; ***crystal*** (15), 4691-700 Westbrook Argonne, Illinois E X ***structure*** Beno D; Huberman E; Argonne National DUPLICATE 60439-4833, of bacterial USA...

Journal code ISSN: 0006-2960.

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**Streptococcus pyogenes: EN, enzymology*

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Dehydrogenase: ME,

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American Cyanamid Co; EP 0608722 A 1994
Balzarini And De Clercq; BIOCHEMICAL JOURNAL 1992, V287, P785
Carr; JOURNAL OF BIOLOGICAL CHEMISTRY 1993, V268(36), P27286 CAPLUS
Pankiewicz; PHARMACOLOGY AND THERAPEUTICS 1997, V76(1-3), P89 CAPLUS

Vertex Pharma; WO 9741211 A 1997

II V Ω.

IT 67 Comparison partial structures domains: and a cystathione beta-synthase (CBS) dimer domain of far unknown function. Using information provided by sequence alignments and the ***crystal*** ***structure***, we prepared several site-specific mutants to examine the role of various active site region. agents, we have expr pathogenic bacterium catalytic e related by a attractive target for acid and the of their in catalysis these differ between results show basis for th Characterist inosine-5'-m f the ***pyogene * * * IMPDH * that 1 OF bacte the distinct ement and indicate there are significant differences in the nonophosphate dehydrogenase. bacterial and mammalian lave expressed and characterized
lacterium ***Streptococcus*** rial enzyme at catalyzes the vironment of bacterial and mammalian ics and that the biochemical and kinetic characteristics of S.

IMPDH are similar to other bacterial *** ***IMPDH*** is a tetramer with its four subunits crystallographic 4-fold axis. The protein is composed of two These variants implicate the. evaluation of MEDLINE enzymes. However, the rack or come of the differences for NAD (1180 microM) exemplify some of the differences making it and mammalian ***IMPDH*** enzymes, making it is the basis for **dehydrogenase*** properties and contribute structure of bacterial from eukaryotic organisms will provide we determined the antimicrobial agents. ***crystal*** first 1.9 A with substrate bound in the catalytic t step unique are lack of sensitivity to mycophenolic similar to other bacterial ***crystal*** * * * IMPDH * * * **structure** * * * IMPDH * * * inhibitors as antimicrobial
IMPDH from the PDH*** enzymes, making i To evaluate the basis for to the to GTP synthesis. ***pyogenes *** provide an explanat design of specific * * HUGWI * * * flap as an essential DUPLICATE with the known ***structure*** of bacterial from the explanation domain of so To provide enzymes Our (19ID) an

H Η T ဌ H TI Ţ TS L4 TI 9028-93-7, Molecular cloning Neurospora study); RL: ANT 118-00-3, Drosophila Eukaryote (Eukaryotae) Bacillus subtilis Escherichia coli the of exogenous an essential enzyme Method to identify specific inhibitors of ***monophosphate*** ***dehydrogenas (Biological study) Bacteria other the pJF118EH expression vector. illustrate the utility purine nucleotide synthesis enzyme, inhibitor host identification of ANSWER 1 OF 7 (serani; method to ***monophosphate***
-00-3, Guanosine, b ***inosine***
IMPDH **Streptococcus** * * * HDDH * * * (method to identify specific inhibitors of
monophosphate ***dehydrogenase** * * * HUGWI * * * (IMP-encoding gene **Streptococcus*** BSU (Biological (method to identify specific inhibitors (expression host; (H712, expression ***inosine*** identification of inhibitors specific **monophosphate*** **inosine*** **IMPDH*** screening systems invention causes expressed in a BIOL (Insecta) (Analyte); BSU (Biological (Eubacteria) ***inosine*** d is an important therapeutic target. (Biological study) commonly used for the expression. guanosine ***Inosine*** relates to methods to identify specific inhibitors of the ide synthesis enzyme, ***IMPDH*** is CAPLUS specific inhibitors of study, found in all free-living organisms from humans to biological studies host; method to identify specific inhibitors

monophosphate ***dehydrogenase*** method to identify specific inhibitors of
monophosphate ***dehydrogenase* identify specific functional form in as a control component COPYRIGHT 2000 ACS cell the ***dehydrogenase*** unclassified); ***dehydrogenase*** ***pyogenes** **dehydrogenase*** ' specific inhibitors
'dehydrogenase*** (invention, ***monophosphate*** proliferation. **monophosphate***
ssified); PRP (Pro A variety of eukaryotic or prokaryotic study, the any a recombinant host cell unclassified); for 0f ***inosine** coding sequence of human and ***dehydrogenase*** of the methods allows for (Properties); * * * IMPDH * * * *dehydrogenase* * * IMPDH * * * ***inosine*** ***inosine** * * * HMPDH * * * of ***INPDH*** The invention allows the ***IMPDH*** * * IMPDH * * prodn. ***dehydrogenase*** ***dehydrogenase*** ***inosine*** ANST (Analytical BIOL were cloned into enzyme which Utilization rather than of. of of.

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Fcollart@anl Laboratory,

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Zhang R; Evans G; Rotella F J;

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***monophosphate** 13789 66589 'MEDLI ' HOME 4033 NE, BIOSIS, CAPLUS, EMBASE, LIFESCI, SCISEARCH, TOXLINE, CANCERLIT, ESBIOBASE' ENTERED AT 13:33:43 ON 16'OCT 2000 SIMPDH OR (INOSINE (W) MONOPHOSPHATE (W) DEHYDROGENASE? to identify specific L5 AND ((CRYSTAL OR X-RAY OR (X(W)RAY)) (3W) STRUCTUR?)
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this enzyme suggests its therapeutic the development of antimicrobial age
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SO ĄU L12 TI Borrelia burgdorferi enzymes. Tritrichomonas foetus, available. substrate site (e.g. CURRENT MEDICINAL CHEMISTRY, (1999 Journal code: CO2. ISSN: 0929-8673. amino acid catalytic interface. potentially inactivation suffer from the NAD-dependent hoth Goldstein B binding. ANSWER 3 OF signature Elucidation Analysis of subunit the those likely identify sequence signatures associated with bacterial or consequence sequence rational characteristics that are different than the mammalian enzymes, suggesting ***IMPDH*** may be an attract: (mycophenolic acid and thiazole-4-carboxamide adenine dinucleotide). monophosphate. Several classes * * * IMPDH * ***IMPDH* which **crystal barrels, bacteri antileukemic and immunosuppressive therapy. structures*** Inosine ₩e interactions, the active s of sequence alignments foundation nalian or bacterial enzyme signature is a prerequisite for the identification of agents that specifically target the bacterial we used sequence alignments of ***IMPDH*** proteins to signatures identified by this residues conserved in all enzymes and a secondary pattern of conservation associated with the major phylogenetic groups. These include structures of the human type II, hamster, NAD nicotinamide ring to he substrate and ggesting ***IMPDH*** may be an attractive target for the of antimicrobial agents. We suggest that the biochemical and cleft is further bounded by a highly flexible flap and loop more effective isoform-specific agents. Recently, a number of

*** ***structures*** of ***IMPDH*** have become M; Colby T D On some degree of toxicity and/or susceptibility to metabolic . The finding that ***IMPDH*** exists as two isoforms, * * * of the basis for this mammalian/bacterial ıl and mammalian of the variance of specific, * * * IMPDH * * * with the active site located partly at the monomer-monomer e substrate and cofactor bind in a continuous cleft on the to have a role in catalysis using information derived from II) MEDLINE provide insi tion for the of these residues or combination of residues that impart of each barrel. The IMP base is well enzymes. These E.C. oxidation of inosine 5 monophosphate (IMP) to xanthosine Several classes of ***IMPDH*** inhibitors are now in is induced in tumor cells, has led to the search for dehydrogenase*** ***monophosphate*** ment. These include agents that bind at either the ribavirin and mizoribine) or at the NAD site and site-specific mutagenesis. Candidate bacterial 1.1.1.205) the active insight into the catalytic mechanism of this enzyme ***Streptococcus*** enzymes show biochemical development bacterial and mammalian enzymes are (1999 Jul') 6 Each structure crystallizes as a tetramer * * * HQGWI * * * selections were in these regions indicates is recognized as an important target cessive therapy. ***IMPDH*** catal site flap and the NAD binding region. facilitate hydride transfer. : structural aspects of inhibitor of highly specific identifiable amino (7) 519-36. ***dehydrogenase*** ***crystal*** or at the NAD site further refined to discern ***pyogenes*** and kinetic inhibitors are now in positioned Ref: 118 ***IMPDH*** * * * IMPDH * * * inhibitors. a pattern of become catalyzes stack for one 'n

These structures reveal enzyme-ligand

for the design of improved inhibitors.

interactions which suggest